Metastatic Renal Cell Carcinoma in a Child: 11-Year Disease-Free Survival Following Surgery

Ron Grant, MD, FRCPC,[1,2] Cynthia Trevenen, MD, FRCPC,[3] William C. Hyndman, MD, FRCSC,[4] Steven Z. Rubin, MD, FRCS(E), FRCSC,[4] and Max J. Coppes, MD, PhD[1,2]

A child with metastatic renal cell carcinoma (RCC) is presented. This case is unusual in that the patient has remained disease free for 11 years following surgery and only one course of chemotherapy prior to thoracotomy. The management of metastatic RCC is reviewed and the genetic mechanisms leading to its development briefly discussed. **Med. Pediatr. Oncol. 28:201–204** © 1997 Wiley-Liss, Inc.

Key words: renal cell carcinoma; childhood; survival; genetics

INTRODUCTION

Renal cell carcinoma (RCC) represents approximately 2% of all new adult cancers [1]. By contrast, RCC is very rare in children and accounts for less than 0.05% of childhood cancers [2], the most common malignant renal neoplasm of childhood being Wilms' tumor [3,4].

The rarity of childhood RCC has precluded the development of optimal management strategies for its treatment. Nevertheless, the overall survival for children with RCC is estimated to be approximately 65% [5]. Those having localized disease have an excellent outcome with nephrectomy only or, alternatively, with nephrectomy followed by additional radiation therapy and/or chemotherapy. Metastatic childhood RCC, on the other hand, has a poor outcome [5–9]. Here, we report a long-term survivor of metastatic childhood RCC who, except for one course of chemotherapy, was successfully treated with surgery only.

CASE REPORT

A previously well 7-year-old white boy was admitted to the Alberta Children's Hospital with a 2-week history of macroscopic hematuria. His history was unremarkable. In particular, he had not experienced pain nor had the parents noticed an abdominal mass. There had been no weight loss, fever, or night sweats. On physical examination, a large, firm, nontender mass was palpated in the right upper quadrant of the abdomen. No evidence of genitourinary malformations (including varicocele), hemihypertrophy, or aniridia was found. Urinalysis confirmed the hematuria; urinary vanillylmandelic acid and homovanillic acid levels were within normal range. An intravenous pyelogram showed a normal left kidney and a large mass arising from the mid and superior pole of the right kidney. Radiograph of the chest showed a 1.3 cm nodule in the periphery of the lower left lobe, consistent with a metastatic lesion. Subsequently, a computed axial tomography (CAT) scan of the chest confirmed the presence of the lesion in the lower left lung. In addition, a second, 0.6 cm, well-defined nodular density was shown in the right lower lobe posteromedially. In view of the age of the patient, these findings were considered to be consistent with metastatic Wilms' tumor and a diagnostic laparotomy was performed.

At surgery, a large tumor was found, uniformly distending the upper half of the kidney. The left kidney, colon, and liver were inspected and appeared grossly normal. A right-sided radical nephrectomy was performed. Histopathologic examination showed a renal cell carcinoma with infiltration of the capsule. The tumor extensively invaded the renal vasculature. Histopathologically, the tumor consisted predominantly of tubules lined by cells with abundant clear cytoplasm, hyperchromatic nuclei with single distinct nucleoli, and rare mitoses. Based on the criteria proposed by Fuhrman et al. [10], this tumor was assigned a grade 3 (Fig. 1). None of the removed lymph nodes showed evidence of metastatic involvement.

To assess response to chemotherapy, the patient under-

Ron Grant's present address is: Hospital for Sick Children, Toronto, Ontario, Canada.

Steven Z. Rubin's present address is: Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada.

From the Departments of [1]Oncology, [2]Pediatrics, [3]Pathology and [4]Surgery, University of Calgary, Calgary, Alberta, Canada.

*Correspondence to: Dr. Max Coppes, Pediatric Oncology Program, Alberta Children's Hospital, 1820 Richmond Road SW, Calgary, Alberta, Canada T2T 5C7.

Received 28 July 1995; accepted 22 March 1996.

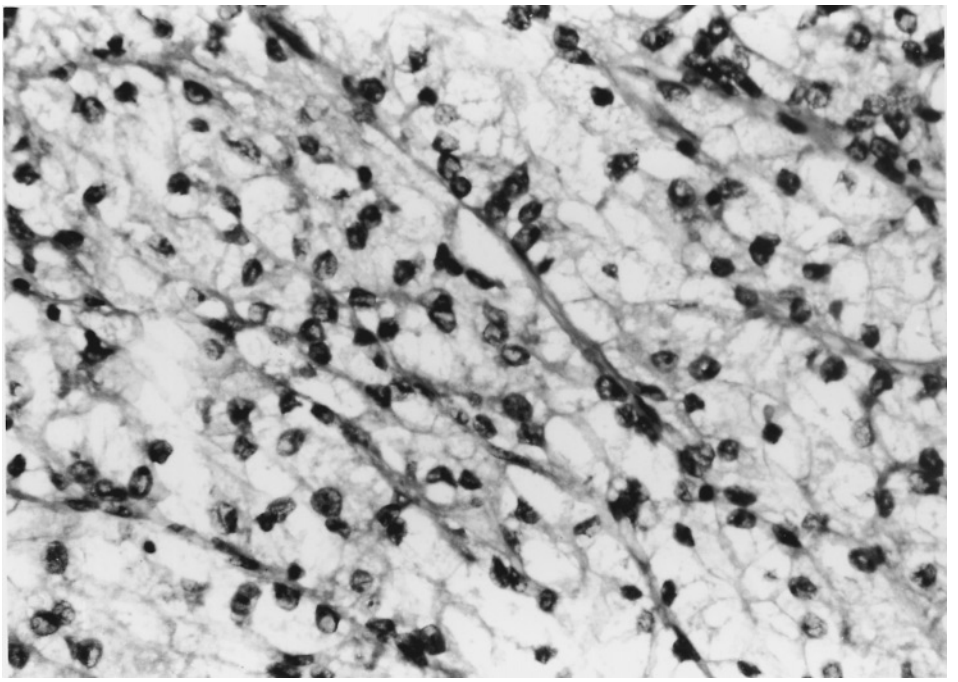

Fig. 1. Renal cell carcinoma with clear cells arranged in cords. Original magnification ×325.

went one course of chemotherapy consisting of doxorubicin (total dose, 45 mg) and vinblastine (4.5 mg). Three weeks later, there were no changes in tumor sizes as determined by a CAT scan of the chest. The patient then underwent a left thoracotomy and wedge resection of the left lower lobe. Histopathologic examination confirmed the presence of metastatic RCC. Two weeks later, a right thoracotomy and right lower lobe medial basilar segmentectomy were performed. Histopathologic examination again confirmed the presence of metastatic RCC. Both metastatic lesions were histologically identical to the primary tumor and showed no evidence of chemotherapy-induced necrosis. The postoperative course following both procedures was unremarkable. In view of the fact that the metastatic lesions had failed to respond to chemotherapy, the parents elected no further treatment. With a follow-up of 11 years, the patient has remained in complete remission.

DISCUSSION

Approximately half of adult patients with RCC have localized disease at diagnosis; the other half has either extensive regional involvement or metastatic spread [11]. Hematogenous spread to either lungs or bones is the most important and most frequent way of tumor dissemination. Based on a limited number of patients, a similar distribution has been noted in childhood RCC [7–9,12].

Because one of the most significant prognostic factors involves the extent of disease, the presence of metastases at presentation correlates with poor survival. In adult patients, metastatic disease at presentation has been associated with a mortality rate of greater than 90% at 3 years, with a median survival time of approximately 10 months. However, if a patient presents with only one pulmonary nodule, resection of the solitary metastatic lesion results in an estimated 5-year survival rate of greater than 45% [13].

Morphologic parameters also have prognostic significance. The grading system proposed by Fuhrman et al. [10] has been demonstrated to be prognostically more effective than other morphologic parameters. In addition, it can be applied to everyday practice. Unlike other grading systems, it is based on nuclear features only distinguishing four groups: grade 1 (with excellent outcome), grades 2 and 3 (with intermediate outcome), and grade 4 (with poor outcome). Our patient was classified as a grade 3 patient, a category associated with a high likelihood of metastases.

Neoadjuvant chemotherapy and/or radiotherapy have generally been ineffective in the treatment of adult RCC. Single-agent therapy has generally yielded response rates of less than 10% [14], with the possible exception of vinblastine therapy with a consistent response rate of approximately 15% [15]. Theoretically, it is possible that childhood RCC has a different biologic behavior than adult RCC and, as a consequence, is more sensitive to chemotherapy and/or radiotherapy. The very limited experience in childhood RCC does not seem to support this hypothesis [8]. In our patient, nonhormonal chemotherapy

TABLE I. Cytogenetic Characteristics of Childhood Renal Cell Carcinomas

Gender	Age (yr)	Cytogenetics	Reference
Male	1.5	46,Y,t(X;17)(p11.2;q25)	22
Male	2	46,Y,t(X;1)(p11.2;q21.2)	27
Male	15	49,Y,t(X;1)(p11.2;q21), + der(X)t(X;1)(p11.2;q21), +5, −16, +17, +18	28
Female	9	46,X,t(X;1)(p11.2;q21)	29
Male	8	46,XY,t(X;17)(p11.2;q25)	30

was used briefly with no evidence of response; both pulmonary metastases remained radiographically unchanged, and following surgical removal no histologic changes were noted compatible with response to presurgical treatment. Therefore, the lack of response to chemotherapy in our patient concurs with the experience reported in adults.

Despite the poor outcome of metastatic RCC, its biologic behavior can be characterized as sometimes unpredictable. Idiopathic tumor regression, which occurs in 0.3–3.4% of RCC cases [16,17], might be secondary to many factors [18]. Most authors agree that host immunity or immunologic resistance plays a role in regulating RCC tumor growth. However, immune function studies conducted on patients with RCC have thus far failed to provide evidence for this hypothesis. Nevertheless, several immunotherapeutic approaches, including the use of cytokines, have been used in an attempt to improve the outcome of metastatic RCC. The best results have been achieved with the combination of interleukin-2 (IL-2) and lymphokine-activated killer (LAK) cells, with an objective response rate of 33% [19], or the combination of IL-2 and interferon-alfa (IFN-α), with a response rate of 36% [20]. The use of biologic response modifiers in childhood RCC is very limited but has generated some guarded optimism [21].

Because RCC is rare in children, information on tumor-specific cytogenetic alterations or loss of function of particular tumor suppressor genes is largely absent [22], unlike for Wilms' tumor [23], the most common childhood renal tumor. In adult RCC, recent studies have shown that the von Hippel-Lindau (*VHL*) gene, located at chromosome 3p25-26, is mutated in approximately 60% of both inherited and sporadic cases [24–26]. *VHL* mutations in childhood RCC have yet to be reported. However, several authors have reported cytogenetic aberrations involving chromosome X band p11.2 in childhood RCC (Table I). Defects involving this chromosomal region have also been reported in adult RCC [28], synovial cell sarcoma [31], acute megakaryoblastic leukemia [32], and leiomyoma [33]. Whether childhood RCC develops by genetic mechanisms distinct from those leading to adult RCC remains to be determined.

The successful management of metastatic RCC remains a therapeutic challenge. We suggest that, until more knowledge is acquired with regard to the biologic behavior of childhood RCC, children presenting with metastatic disease be offered an aggressive surgical approach. Whether IL-2 and/or IFN-α are to be recommended as "best therapy" for advanced childhood RCC [21] remains to be determined.

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